DAYVIGO®

Film-Coated Tablet 5mg, 10mg
<lemborexant>

CONTRAINDICATIONS
(DAYVIGO is contraindicated in the following patients)
1. Patients with narcolepsy
2. Patients with a history of hypersensitivity to the ingredients of this product.
3. Patients with severe hepatic function disorder (plasma lemborexant concentration may increase.)
(see "PHARMACOKINETICS" section)

DESCRIPTION

1. Composition

5 mg tablets: Each pale-yellow film-coated tablet contains 5 mg of lemborexant. Yellow ferric oxide, titanium oxide, magnesium stearate, talc, low substituted hydroxypropylcellulose, lactose hydrate, hydroxypropylcellulose, hypromellose, and macrogol 6000 are also present as inactive ingredients.
10 mg tablets: Each orange film-coated tablet contains 10 mg of lemborexant. Yellow ferric oxide, red ferric oxide, titanium oxide, magnesium stearate, talc, low substituted hydroxypropylcellulose, lactose hydrate, hydroxypropylcellulose, hypromellose, and macrogol 6000 are also present as inactive ingredients.

2. Product description

Brand name	Formulation / Identification code	Appearance			Description
		Top	Bottom	Side	
DAYVIGO Tablet 5mg	film-coated tablets	LEM	5		pale yellow
	LEM 5	Diameter / Mass / Thickness 7.1 mm / 127 mg / 3.3 mm			
DAYVIGO Tablet 10mg	film-coated tablets	LEM	10		orange
	LEM 10	Diameter / Mass / Thickness 7.1 mm / 127 mg / 3.3 mm			

INDICATION(S)

DAYVIGO is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

DOSAGE AND ADMINISTRATION

The usual dosage for adults is 5 mg of lemborexant administered orally once daily immediately before bedtime, with at least 7 hours remaining before the planned time of awakening. The dosage may be adjusted as appropriate according to clinical response and tolerability, but should not exceed 10 mg once daily.

Precautions regarding dosage and administration

1. If dosage should be increased beyond the starting dosage due to insufficient effect, the dose should be increased to 10 mg once daily. Dose escalation beyond the starting dose should be performed with care while closely observing the condition of the patient, as adverse reactions such as somnolence may increase, and dose reduction should be attempted as symptoms improve.

2. Instruct the patient to take DAYVIGO immediately before bedtime. Instruct the patient not to take DAYVIGO if less than 7 hours before the time of planned awakening is possible.

3. Since sleep induction may be delayed, avoid taking DAYVIGO at the same time or right after meals. (With postprandial administration, the plasma lemborexant concentration immediately after the administration may decrease compared to that with administration on an empty stomach.) (see "PHARMACOKINETICS" section)

4. Concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors is contraindicated. The maximum recommended dosage of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors (see "PHARMACOKINETICS" section)

5. Since plasma lemborexant concentration increase in patients with moderate hepatic function disorder, the dosage may not exceed 5 mg once daily in these patients and should be administered with care.

(see "PRECAUTIONS" and "PHARMACOKINETICS" sections)

6. The efficacy and safety of concomitant use with other drugs for treatment of insomnia have not been established.

PRECAUTIONS

1. Careful Administration (DAYVIGO should be administered with care in the following patients):

(1) Patients with mild and moderate hepatic function disorder (plasma lemborexant concentration may increase) (see "PHARMACOKINETICS" section)

(2) Patients with severe renal impairment (plasma lemborexant concentration may increase) (see "PHARMACOKINETICS" section)

(3) Patients with organic brain disorders (effects of DAYVIGO may excessively increase)

(4) Patients with moderate and severe respiratory function disorder (DAYVIGO has never been administered to these patients, and safety has not been established) (see "CLINICAL STUDIES" section)

2. Important Precaution(s)

(1) The effects of DAYVIGO may persist until the next morning (or longer) after ingestion, and this product may induce drowsiness as well as impairment of attention, concentration, and reflex movements, so patients should be cautioned against engaging in potentially hazardous activities such as operating machinery or driving a motor vehicle.

(2) When symptoms improve, consider the necessity of continuing DAYVIGO, and take care that DAYVIGO is not aimlessly administered.

(3) Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms:
Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions, can occur with the use of DAYVIGO. Prescribers should explain the nature of these events to patients when prescribing DAYVIGO.
Symptoms similar to mild cataplexy can occur with DAYVIGO. Such symptoms can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with an identified triggering event (e.g., laughter or surprise).

(4) Worsening of depression/suicidal ideation:
In clinical studies of DAYVIGO in patients with insomnia, the incidence of suicidal ideation or any suicidal behaviour, as assessed by questionnaire, was higher in patients receiving DAYVIGO than in those receiving placebo (0.3% for DAYVIGO 10 mg, 0.4% for DAYVIGO 5 mg, and 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed at any one time.
The emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

(5) Complex sleep behaviours:
Complex sleep behaviours, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics such as DAYVIGO.
These events can occur in hypnotic-naïve as well as in hypnotic- experienced persons. Patients usually do not remember these events.
Complex sleep behaviours may occur following the first or any subsequent use of DAYVIGO, with or without the concomitant use of alcohol and other CNS depressants (see "Drug Interactions" section).
Discontinue DAYVIGO immediately if a patient experiences a complex sleep behaviour.

3. Drug Interactions

Lemborexant is mainly metabolized by the drug-metabolizing enzyme CYP3A. (see "PHARMACOKINETICS" section)

Contraindications for co-administration (Dayvigo should not be co-administered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Moderate and strong CYP3A inhibitors (itraconazole, clarithromycin, erythromycin, fluconazole, verapamil, etc)	These drugs may increase the incidence of adverse reactions.	Inhibition of CYP3A, the enzyme metabolizing lemborexant, leads to increased plasma lemborexant concentrations. (see "PHARMACOKINETICS" section) Co-administration with moderate and strong CYP3A inhibitors is contraindicated.

Recommendations for co-administration with other drugs:

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Weak CYP3A Inhibitors (e.g.ranitidine)	These drugs may increase the effects of DAYVIGO.	Inhibition of CYP3A, the enzyme metabolizing lemborexant, leads to increased plasma lemborexant concentrations. (see "PHARMACOKINETICS" section) The maximum dosage of DAYVIGO is 5mg no more than once per night when co-administered with weak CYP3A inhibitors.
CYP3A inducers (rifampicin, phenytoin, etc)	These drugs may decrease the effects of DAYVIGO.	Induction of CYP3A, the enzyme metabolizing lemborexant, leads to decreased plasma lemborexant concentrations. Concomitant use of rifampicin with DAYVIGO lead to a decrease in the blood concentration of lemborexant. C_{max} and $AUC_{(0-inf)}$ of lemborexant were decreased by 92% and 97% compared to those with lemborexant alone, respectively. (see "PHARMACOKINETICS" section) Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers.
Central nervous depressants : Phenothiazine derivatives Barbiturate derivatives, etc.	DAYVIGO may enhance the depressant effects to central nervous system. These drugs should be administered with care.	DAYVIGO and these drugs have depressant effects to the central nervous system, so may enhance the effects of each other.
Alcohol (drinking)	Since additive decreases in psychomotor functions may occur, instruct the patient to refrain from drinking alcohol while being treated with DAYVIGO.	Concomitant use of alcohol with DAYVIGO leads to increased plasma lemborexant concentrations. Since alcohol has suppressive effects on the central nervous system, an additive effect may occur. (see "PHARMACOKINETICS" section)

4. Adverse Reaction(s)

Adverse reactions were reported in 249 (28.2%) of the 884 patients (including 155 Japanese patients) who received lemborexant in an international phase III study involving patients with insomnia.

Major adverse reactions included somnolence in 95 patients (10.7%), headache in 37 patients (4.2%), and malaise in 27 patients (3.1%).

(1) Other adverse reaction(s)

System Organ Class	≥3%	≥1 and <3%	<1%	Incidence unknown
Nervous system disorders	somnolence and headache	dizziness and sleep paralysis	disturbance in attention	N/A
Psychiatric disorders	N/A	abnormal dreams and nightmares	hallucinations, confusional state	parasomnias Note1)
Cardiovascular	N/A	N/A	palpitations	N/A
Gastrointestinal	N/A	nausea	dry mouth and abdominal pain	N/A
Hepatic	N/A	N/A	ALT (GPT) increased	N/A
Sensory organs	N/A	N/A	vertigo and tinnitus	eye pain Note2)
Other	malaise	weight increased	increased appetite, hyperhidrosis, blood triglycerides increased, feeling abnormal, fall, myalgia	N/A

Note1) adverse reaction reported in spontaneous reports
Note2) adverse reaction reported in overseas clinical study

5. Use in the Elderly

A pharmacokinetic study involving the elderly has revealed a tendency towards increases in plasma concentrations in the elderly compared to those in non-elderly individuals. Given that physiological functions of the elderly are decreased in general, administer DAYVIGO carefully while monitoring the status of the patient. (see "PHARMACOKINETICS" section)

6. Use during Pregnancy, Delivery or Lactation

(1) Pregnant or possibly pregnant women should receive DAYVIGO only when the benefit of treatment is considered to outweigh the risks. (Safety of use during pregnancy has not been established.)
(2) Avoid treating lactating women with DAYVIGO. When there is no other choice but to administer the drug, instruct them to stop breastfeeding. (Lemborexant and its metabolites transfer to breast milk in lactating rats.)

7. Pediatric Use

Clinical study in pediatric patients has not been performed.

8. Overdosage

(1) Symptoms and signs
Little information exists regarding DAYVIGO overdose. A dose-dependent increase in the incidence of somnolence was reported in an overseas clinical study of DAYVIGO administered up to 75 mg to healthy adult subjects.
Hypotonia, photopsia, hypoxia, initial insomnia, coldness, etc. were reported in clinical studies of DAYVIGO administered at >10 mg.
(2) Treatment
No specific antidote exists for the treatment of DAYVIGO overdose. Common symptomatic therapy should be provided in the event of overdose.

9. Precautions Concerning Use

At the time of drug delivery:
Instruct the patient to take the drug in the press-through package (PTP) out of the PTP sheet before taking it. Accidental ingestion of a PTP sheet may lead to damage to the esophageal mucous membrane by hard, sharp edges, and furthermore, may cause perforation resulting in serious complications such as mediastinitis.

PHARMACOKINETICS

1. Plasma concentration

The plasma concentration-time profile after administration of DAYVIGO 10 mg on Day 14 in healthy Japanese adult males who received the drug repeatedly for 14 days at 2.5, 10 or 25 mg once daily is shown in Figure 1. The pharmacokinetic parameters at Day 1 and Day 14 in those who received DAYVIGO 2.5 mg and 10mg are shown in Table 1. The maximum concentration (C_{max}) and area under the concentration-time curve from 0 to 24 hours ($AUC_{(0-24h)}$) of lemborexant increased with increasing dose. C_{max} was 70.2 ng/mL, and plasma lemborexant concentrations at 3 and 8 hours postdose were 31.4 ng/mL and 17.9 ng/mL, respectively, on Day 14 after administration of 10 mg.

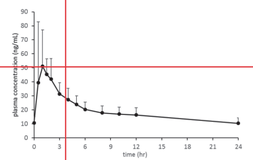

Figure 1 Plasma concentration-time profile after administration of DAYVIGO 10 mg on Day 14 in healthy adult (Mean+standard deviation)

Table 1 Pharmacokinetic parameters with repeated administration

Dose (mg)	Period of administration	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-24h)}$ (ng·h/mL)	t½ (h)
2.5	Day 1	10.0 (1.36)	1.5 (1.0-4.0)	54.8 (13.1)	-
	Day 14	13.2 (3.40)	1.3 (0.5-2.0)	95.6 (21.4)	50.6 (11.4)
10	Day 1	46.5 (25.8)	1.0 (0.5-6.0)	231 (40.2)	-
	Day 14	70.2 (30.2)	1.5 (0.5-2.0)	459 (110)	47.4 (13.9)

All values are shown as mean (standard deviation), except for t_{max}, which is shown as median (minimum value-maximum value).
2.5 mg and 10 mg: n=6

2. Effects of meals

In 24 healthy adults who received DAYVIGO at 10 mg orally as a single dose, the geometric mean ratios (fed/fasted) with 90% confidence intervals (CIs) for C_{max} and $AUC_{(0-t)}$ of lemborexant were 0.771 (0.687, 0.866) and 1.18 (1.09, 1.28), respectively. C_{max} was 23% lower and $AUC_{(0-t)}$ was 18% higher under fed conditions compared with fasted conditions. Furthermore, t_{max} (median) was delayed by 2 hours. The terminal elimination half-life (mean) of lemborexant was 50.8 h under fasted conditions and 53.8 h under fed conditions (see "Precautions regarding dosage and administration" section)

3. Distribution

The plasma protein binding (*in vitro* in human plasma) was 87.4-88.7% at concentrations of 100 to 1000 ng/mL.

4. Metabolism

Lemborexant was mainly eliminated from the body through metabolism, with the metabolite with systemic exposure greater than 10% of total drug-related exposure being M10 (N-oxide) alone (13%). M10 was confirmed to contribute to a lesser extent to the pharmacological effects than lemborexant.
An in vitro metabolism study showed that CYP3A is mainly involved in the metabolism of lemborexant. Furthermore, M10 was shown to be generated by oxidative metabolism of lemborexant via CYP3A.

5. Excretion

In 8 healthy adult males who received C-labelled lemborexant at 10 mg orally as a single dose, the total recovery rate for radioactivity was 86.5%, with 57.4% excreted in feces and 29.1% in urine.

6. Special population

(1) Elderly
In 5 healthy elderly subjects (66-76 years) who received DAYVIGO repeatedly for 14 days at 25 mg once daily, geometric mean ratios (healthy elderly/healthy adult) with 90% confidence intervals for C_{max} and $AUC_{(0-24h)}$ of lemborexant on Day 14 were 1.18 [0.770, 1.79] and 1.12 [0.762, 1.64], respectively. C_{max} and $AUC_{(0-24h)}$ were 18% and 12% higher in elderly subjects than in healthy adult subjects, respectively. The terminal elimination half-life (mean) of lemborexant was 49.6 h in healthy adult subjects and 60.1 h in healthy elderly subjects. In population pharmacokinetic analysis involving healthy adult subjects and patients with insomnia in phase I-III clinical studies, apparent clearance of lemborexant was 26% lower in elderly subjects (≥65 years old). (see "Use in the Elderly" section)

(2) Patients with hepatic function disorder
In 8 patients with mild hepatic function disorder (Child-Pugh score: 5-6) and 8 patients with moderate hepatic function disorder (Child-Pugh score: 7-9) who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (patients with hepatic function disorder/healthy adults) with 90% CIs for C_{max} of lemborexant were 1.58 [1.18, 2.11] and 1.22 [0.915, 1.63], respectively, and those for $AUC_{(0-inf)}$ were 1.25 [0.880, 1.78] and 1.54 [1.06, 2.22], respectively. C_{max} was 58% and 22% higher and $AUC_{(0-inf)}$ was 25% and 54% higher in patients with mild hepatic function disorder and those with moderate hepatic function disorder, respectively, than in healthy adults. The terminal elimination half-lives (mean) of lemborexant were 69.0 h, 78.7 h and 108 h in healthy adult subjects, patients with mild hepatic function disorder and those with moderate hepatic function disorder, respectively. Geometric mean ratios (patients with hepatic function disorder/healthy adults) with 90% CIs for C_{max} of the main metabolite M10 were 0.947 [0.684, 1.31] and 0.766 [0.552, 1.06], respectively, and those for $AUC_{(0-inf)}$ of M10 were 0.950 [0.703, 1.28] and 1.04 [0.754, 1.42], respectively.

C_{max} was slightly lower in patients with mild and moderate hepatic function disorder than in healthy adults, but $AUC_{(0-inf)}$ was similar between these patients and healthy adult subjects. The terminal elimination half-lives (mean) of M10 were 64.3 h, 66.6 h and 91.2 h in healthy adults, patients with mild hepatic function disorder and those with moderate hepatic function disorder, respectively. No study of pharmacokinetics has been conducted in patients with severe hepatic function disorder (Child-Pugh score: 10-15). (see "CONTRAINDICATIONS" and "Careful Administration" sections)

(3) Patients with renal impairment
In 8 patients with severe renal impairment (estimated glomerular filtration rate [eGFR] by MDRD equation, 15-29 mL/min/1.73 m^2) who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (patients with renal impairment/healthy adults) with 90% CIs for C_{max} and $AUC_{(0-inf)}$ of lemborexant were 1.05 [0.774, 1.42] and 1.50 [1.13, 1.99], respectively. C_{max} and $AUC_{(0-inf)}$ were 5% and 50% higher in patients with severe renal impairment than in healthy adults, respectively. The terminal elimination half-lives (mean) of lemborexant were 70.0 h and 74.8 h in health adults and patients with severe renal impairment, respectively. Geometric mean ratios (patients with renal impairment/healthy adults) with 90% CIs for C_{max} and $AUC_{(0-inf)}$ of the main metabolite M10 were 0.725 [0.481, 1.09] and 1.36 [0.982, 1.90], respectively. C_{max} was 28% lower and $AUC_{(0-inf)}$ was 36% higher in patients with severe renal impairment than in healthy adults, respectively. The terminal elimination half-lives (mean) of M10 were 64.0 h and 64.7 h in healthy adults and patients with severe renal impairment, respectively. (see "Careful Administration" section)

7. Drug interactions

(1) Itraconazole (Strong CYP3A Inhibitor)
In 15 healthy adults on itraconazole at 200 mg once daily as repeated doses who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for Cmax and $AUC_{(0-inf)}$ of lemborexant were 1.36 [1.18, 1.57] and 3.70 [3.18, 4.31], respectively. C_{max} and $AUC_{(0-inf)}$ of lemborexant were 36% and 270% higher with combination therapy than those with monotherapy, respectively. Terminal elimination half-lives (mean) of lemborexant with monotherapy and combination therapy were 54.4 h and 118 h, respectively. Geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0-inf)}$ of M10 were 0.130 [0.107, 0.158] and 0.626 [0.465, 0.844], respectively. The terminal elimination half-lives (mean) of M10 with monotherapy and combination therapy were 48.1 h and 150 h, respectively. (see "Precautions regarding dosage and administration" and "Drug Interactions" sections)

(2) Fluconazole (Moderate CYP3A Inhibitor)
In 14 healthy adults on fluconazole at 200 mg once daily as repeated doses who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for Cmax and $AUC_{(0-inf)}$ of lemborexant were 1.62 [1.34, 1.97] and 4.17 [3.83, 4.55], respectively. C_{max} and $AUC_{(0-inf)}$ of lemborexant were 62% and 317% higher with combination therapy than those with monotherapy, respectively. The terminal elimination half-lives (mean) of lemborexant with monotherapy and combination therapy were 55.4 h and 99.5 h, respectively. Geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0-inf)}$ of M10 were 0.580 [0.513, 0.657] and 2.33 [1.73, 3.14], respectively. Terminal elimination half-life (mean) of M10 with monotherapy and combination therapy were 45.5 h and 78.6 h, respectively. (see "Precautions regarding dosage and administration" and "Drug Interactions" sections)

(3) Rifampicin (Strong CYP3A Inducer)
In 15 healthy adults on rifampicin at 600 mg once daily as repeated doses who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0-inf)}$ of lemborexant were 0.085 [0.067, 0.107] and 0.034 [0.026, 0.045], respectively. Cmax and $AUC_{(0-inf)}$ of lemborexant were 92% and 97% lower with combination therapy than those with monotherapy, respectively. The terminal elimination half-lives (mean) of lemborexant with monotherapy and combination therapy were 45.6 h and 10.8 h, respectively. Geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0-inf)}$ of M10 were 1.00 [0.884, 1.13] and 0.127 [0.112, 0.145], respectively. The terminal elimination half-lives (mean) of M10 with monotherapy and combination therapy were 39.4 h and 4.07 h, respectively. (see "Drug Interactions" section)

(4) Midazolam (Sensitive CYP3A Substrate)
In 28 healthy adults on DAYVIGO at 10 mg once daily as repeated doses who received midazolam at 2 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and AUC(0-inf) of midazolam were 1.13 [1.03, 1.24] and 1.13 [1.02, 1.25], respectively. C_{max} and $AUC_{(0-inf)}$ of midazolam were 13% and 13% higher with combination therapy than those with monotherapy, respectively. The terminal elimination half-lives (mean) of midazolam with monotherapy and combination therapy were 4.00 h and 4.21 h, respectively.

(5) Alcohol
In 21 healthy adults on DAYVIGO at 10 mg once daily as a single dose, concomitant intake of alcohol resulted in additive declines in cognition. Moreover, geometric mean ratios (with concomitant intake of alcohol/without concomitant intake of alcohol) with 90% CIs for C_{max} and $AUC_{(0-72h)}$ of lemborexant were 1.35 [1.14, 1.60] and 1.70 [1.54, 1.89], respectively. C_{max} and $AUC_{(0-72h)}$ of lemborexant were 35% and 70% higher with concomitant intake of alcohol than without concomitant intake of alcohol, respectively. The terminal elimination half-lives (mean) of lemborexant were 33.9 h and 29.9 h with and without concomitant intake of alcohol, respectively. (see "Drug Interactions" section)

Note: The maximum approved dose of DAYVIGO is 10 mg.

CLINICAL STUDIES

1. Phase III clinical studies (Study 303 and Study 304)

Lemborexant was evaluated for efficacy and safety in 2 clinical trials (each with >900 patients) in patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.
The efficacy and safety of lemborexant was evaluated in Study E2006-G000-303 (Study 303), a randomized, double-blind and placebo-controlled 6month sleep diary study, followed by an additional 6 months of blinded active treatment period where all patients received lemborexant. Study E2006-G000-304 (Study 304) was a 1-month, randomized, double-blind, placebo- and zolpidem tartrate extended release-controlled, parallel-group polysomnography (PSG) and sleep diary study. In both studies, adult patients (mean age 51.8 years; 714 females, 213 males) were treated with lemborexant 5 mg (n=467) or 10 mg (n=460). Elderly patients (≥65 years; mean age 70.4 years, 342 females, 149 males) were treated with lemborexant 5 mg (n=246) or 10 mg (n=245).
In Study 303 and Study 304, as measured by subjective and/or objective methods, lemborexant led to significantly larger decreases (improvements) in both the time needed to fall asleep and the amount of time spent awake during the night after sleep onset compared to placebo, and significantly larger increases in sleep efficiency (time spent asleep/time spent in bed) compared to placebo, all of which were sustained through 6 months (Tables 2, 3, & 4).
In Study 304, lemborexant 5 mg and 10 mg led to significantly larger decreases in sleep onset (latency to persistent sleep [LPS]) and wake after sleep onset (WASO) during the full sleep period and during the second half of the sleep period) compared to placebo as assessed objectively by PSG. Lemborexant led to significantly larger increases in sleep efficiency (SE) compared to placebo (Table 4). As measured by PSG, lemborexant 5 mg and 10 mg led to significantly larger decreases in sleep onset (LPS), WASO across the entire night, and WASO in the second half of the night compared with zolpidem tartrate extended release (ER). The statistically significant effects of lemborexant on patient-reported (subjective) sleep onset and sleep maintenance (sWASO and sSE) after the first 7 nights of treatment remained statistically significant compared with placebo through 6 months (Study 303). The efficacy of lemborexant was similar between women and men, adult and elderly, and between Caucasians and non-Caucasians.

Table 2: Sleep Diary Assessments of Sleep Parameters in Study 303 and 304

	Placebo n=527	Lemborexant 5 mg n=582	Lemborexant 10 mg n=584	Difference between Lemborexant and Placebo	
				Lemborexant 5 mg	Lemborexant 10 mg
Sleep Onset (sSOL), minutes					
Baseline (median)	54	56	55		
First 7 Days Median Change from Baseline	-3	-13	-14	-10	-11
LSGM Ratio	0.871	0.692	0.653	0.794***	0.750***
Month 1 Median Change from Baseline	-5	-16	-18	-11	-13
LSGM Ratio	0.776	0.611	0.571	0.788***	0.736***
Sleep Maintenance (sSE), %					
Baseline (mean)	59	60	59		
First 7 Days LSM Change from Baseline	5	9	11	4***	6***
Month 1 LSM Change from Baseline	8	11	12	3***	5***
Sleep Maintenance (sWASO), minutes					
Baseline (mean)	147	148	155		
First 7 Days LSM Change from Baseline	-17	-30	-38	-13***	-21***
Month 1 LSM Change from Baseline	-28	-36	-41	-8*	-13***

LSGM: Least squares geometric mean; LSM: Least squares mean
*P <0.05
**P <0.01
***P <0.001

0mm 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200

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APPROVAL SIGNATURE

DATE

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Item No.	2006065
EML	EML-DAYV-2300027
Description	Dayvigo
Strength	All
Change Description	Address Change
Component Type	Leaflet
Dimensions	395 x 696 mm
Keyline Reference	LEAF020 V 07
Varnish	
Market(s)	NON EU: SINGAPORE
Language(s)	English
Barcode Type	:
Pharmacode	4981
Proof By	SBL
Proof Number	1
Main Body Font Size	9pt
Printed Colours	1
Date	23/05/2023

PRINTING COLOURS
Black

TECHNICAL COLOURS
Back Panel (Tech)
Front Panel (Tech)
Keyline (Non-Printing)
Text Free Area (Tech)
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Table 3: Sleep Diary Assessments of Sleep Parameters Through Month 6 in Study 303

	Placebo n=318	Lemborexant 5 mg n=316	Lemborexant 10 mg n=315	Difference between Lemborexant and Placebo	
				Lemborexant 5 mg	Lemborexant 10 mg
Sleep Onset (sSOL), minutes					
Baseline (median)	56	54	56		
Week 1 Median Change from Baseline	-3	-11	-12	-8	-9
LSGM Ratio	0.931	0.728	0.701	0.781***	0.752***
Month 1 Median Change from Baseline	-7	-14	-20	-7	-13
LSGM Ratio	0.786	0.637	0.605	0.810***	0.770***
Month 3 Median Change from Baseline	-11	-21	-26	-10	-15
LSGM Ratio	0.673	0.524	0.518	0.778***	0.770***
Month 6 Median Change from Baseline	-11	-22	-28	-11	-17
LSGM Ratio	0.618	0.453	0.433	0.732***	0.701***
Sleep Maintenance (sSE), %					
Baseline (mean)	61	63	62		
Week 1 LSM Change from Baseline	2	6	8	4***	6***
Month 1 LSM Change from Baseline	6	8	9	2***	4***
Month 3 LSM Change from Baseline	9	13	13	4***	4***
Month 6 LSM Change from Baseline	10	14	14	5***	5***
Sleep Maintenance (sWASO), minutes					
Baseline (mean)	133	133	137		
Week 1 LSM Change from Baseline	-5	-19	-21	-14***	-17***
Month 1 LSM Change from Baseline	-17	-23	-24	-6	-7
Month 3 LSM Change from Baseline	-27	-40	-37	-13**	-10*
Month 6 LSM Change from Baseline	-29	-47	-42	-17***	-13*

LSGM: Least squares geometric mean; LSM: Least squares mean
**P <0.05*
***P <0.01*
****P <0.001*

Table 4: Polysomnographic Assessments of Sleep Parameters in Study 304

	Placebo n=208	Lemborexant 5 mg n=266	Lemborexant 10 mg n=269	Difference between Lemborexant and Placebo		ZOL ER n=262	Difference between Lemborexant and ZOL ER	
				Lemborexant 5 mg	Lemborexant 10 mg		Lemborexant 5 mg	Lemborexant 10 mg
Sleep Onset (LPS), minutes								
Baseline (median)	44	45	45			45		
Days 1/2 Median Change from Baseline	-6	-17	-19	-11	-13	-13	-4	-6
LSGM Ratio	0.763	0.649	0.607	0.850**	0.795***	0.742	0.874*	0.818***
Month 1 Median Change from Baseline	-8	-20	-21	-12	-13	-8	-12	-13
LSGM Ratio	0.699	0.541	0.506	0.773***	0.723***	0.852	0.634***	0.594***
Sleep Maintenance (SE), %								
Baseline (mean)	69	68	68			68		
Days 1/2 LSM Change from Baseline	5	14	17	9***	12***	12	2**	5***
Month 1 LSM Change from Baseline	6	13	14	7***	8***	10	4***	5***
Sleep Maintenance (WASO), minutes								
Baseline (mean)	112	113	115			114		
Days 1/2 LSM Change from Baseline	-18	-51	-60	-33***	-42***	-45	-6*	-15***
Month 1 LSM Change from Baseline	-21	-45	-47	-24***	-25***	-38	-8**	-9**
Sleep Maintenance (WASO2H), minutes								
Baseline (mean)	74	77	77			7		
Days 1/2 LSM Change from Baseline	-9	-30	-37	-22***	-28***	-24	-6**	-13***
Month 1 LSM Change from Baseline	-11	-27	-29	-16***	-18***	-21	-7**	-8***

LSGM: Least squares geometric mean; LSM: Least squares mean; ZOL ER: zolpidem extended-release
**P <0.05*
***P <0.01*
****P <0.001*

2. Clinical pharmacology studies

(1) Effects on driving performance (Study 106)
A total of 24 healthy adult male/female subjects (median age, 49 years), including 1 Japanese subject, and 24 healthy elderly male/female subjects (median age, 67 years) received DAYVIGO 5 or 10 mg before bedtime and were evaluated for effects on driving performance the next morning (approximately 9 h after taking the drug). With DAYVIGO administered at 5 or 10 mg over 8 days, no statistically significant effects on driving performance after one or multiple doses were noted in either healthy adult or healthy elderly subjects as compared to placebo,although driving performance was slightly impaired in subjects receiving DAYVIGO 10 mg than in those receiving DAYVIGO 5 mg.

(2) Effects on postural stability and cognitive functions during the night and the next morning (Studies 108 and 304)
Healthy subjects (≥55 years old) received DAYVIGO 5 or 10 mg before bedtime and were evaluated for the effects on postural stability and cognitive functions (attention and memory) upon awakening during the night (approximately 4 h after administration of DAYVIGO) and upon awakening the next morning (approximately 8 h after administration of DAYVIGO). Approximately 4 h after administration of DAYVIGO, as compared with placebo, increased body sway was noted with DAYVIGO 5 and 10 mg, and decreased attention and memory were noted with DAYVIGO 10 mg. Moreover, in patients with insomnia (≥55 years old) receiving DAYVIGO 5 or 10 mg before bedtime, decreased attention was noted upon awakening the next morning (approximately 8 h after administration) with DAYVIGO 5 and 10 mg, as compared with placebo.
There was no effect of DAYVIGO on tests of memory or body sway in the morning.

(3) Respiratory Safety (Study 102)
In a study of healthy adult and elderly patients, there were no differences between placebo and lemborexant 10 mg and 25 mg with respect to oxygen saturation during sleep. In a study of patients with mild sleep apnea, there was no effect of lemborexant on the apnea-hypopnea index when compared with placebo following single and multiple doses of lemborexant 10 mg.
(see "Careful Administration" section)

(4) Effects on drug abuse (Study 103)
With administration of DAYVIGO at 10, 20 or 30 mg in healthy adults (n=39) with experience of drug abuse, subjective assessments regarding DAYVIGO drug preference and other tendencies toward abuse were higher than those with placebo and similar to those with zolpidem at 30 mg and suvorexant at 40 mg.
Because individuals with a history of abuse or addiction to alcohol or other drugs may be at increased risk for abuse and addiction to DAYVIGO, follow such patients carefully.

Note: The maximum approved dose of DAYVIGO is 10 mg.

NON-CLINICAL TOXICOLOGY

1. Fertility

Lemborexant was orally administered to female rats at doses of 30, 100, or 1000 mg/kg/day prior to and throughout mating and continuing to gestation Day 6. These doses are approximately 12 to >500 times the MRHD based on AUC. Irregular estrous cycles and decreased pregnancy rate were observed at 60 times the MRHD based on AUC, and decreased numbers of corpora lutea, implantations, and live embryos were observed at >500 times the MRHD based on AUC. The exposure at the NOAEL of 30 mg/kg/day is approximately 12 times the MRHD based on AUC. Lemborexant did not affect fertility when orally administered to male rats at doses of 30, 100, or 1000 mg/kg/day prior to and throughout mating; the highest dose is approximately 138 times the MRHD based on AUC.

2. Carcinogenesis

Lemborexant did not increase the incidence of tumors in rats treated for 2 years at oral doses of 30, 100, and 300 mg/kg/day (males) and 10, 30, and 100 mg/kg/day (females), which are >80 times the MRHD based on AUC. Lemborexant did not increase the incidence of tumors in Tg ras H2 mice treated for 26 weeks at oral doses of 50, 150, and 500 mg/kg/day.

3 Mutagenesis

Lemborexant was neither mutagenic nor clastogenic in a standard battery of in vitro and in vivo genotoxicity studies.

4. Animal Toxicology and/or Pharmacology

Lemborexant administered to mice at oral doses of 10 or 30 mg/kg resulted in behavior characteristic of cataplexy when presented with chocolate. Chocolate is a stimulus that has been demonstrated to increase cataplexy occurrences in narcoleptic mice.

RISK OF DEPENDENCE

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. In animal studies and clinical trials evaluating physical dependence, chronic administration of lemborexant did not produce withdrawal signs or symptoms upon drug discontinuation. This suggests that lemborexant does not produce physical dependence.

PHARMACOLOGY

1. Mechanism of action

In a calcium influx assay, Ki values of lemborexant for human orexin receptor types 1 (OX1) and 2 (OX2) were 8.1 nmol/L and 0.48 nmol/L, respectively. The metabolite M10, which can be found in human plasma, displayed binding affinity at orexin receptors comparable to that of unchanged drug.
Lemborexant is presumed to shift the brain from wakefulness state to sleep state by reversibly blocking the binding of wake-promoting neuropeptides orexin A and orexin B to the receptors OX1 and OX2, thereby inducing sleep.

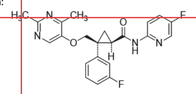
2. Effects on sleep

Lemborexant reduced sleep latency and increased total sleep time in rats. No significant difference was noted in the ratio of rapid eye movement (REM) sleep time to total sleep time.

PHYSICOCHEMISTRY

Nonproprietary name: Lemborexant
Chemical name: (1*R*,2*S*)-2-[[(2,4-dimethylpyrimidin-5-yl)oxy] methyl]-2-(3-fluorophenyl)-*N*-(5-fluoropyridin-2-yl) cyclopropanecarboxamide

Molecular formula: $C_{22}H_{20}F_2N_4O_2$
Molecular weight: 410.42
Structural formula:



Description: Lemborexant occurs as a white powder and is freely soluble in methanol or benzyl alcohol, soluble in ethanol (99.5), and practically insoluble in water.
Melting point: 177°C
Partition coefficient: 3.7

STORAGE CONDITION
Store at or below 30°C

SHELF LIFE
36 months

PACKAGING
5mg: 28 film-coated tablets
10mg: 28 film-coated tablets
(PVC/aluminum foil blister, 14 tablets per sheet, 2 sheets per box)

PRODUCT REGISTRANT
Eisai (Singapore) Pte. Ltd.
152 Beach Road,
#15-07 to 08 Gateway East,
Singapore 189721

DATE OF REVISION OF PACKAGE INSERT

April 2023

Eisai Ltd.

FRONT PANEL

DAYVIGO®
Film-Coated Tablet 5mg, 10mg
<Lemborexant>

BACK PANEL

2006065

PHARMA CODE
READ DIRECTION

0mm 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200

Cirrus
16 East Park Road | Leicester | LE5 4QA | UK

APPROVAL SIGNATURE

DATE

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Item No.	2006065
EML	EML-DAYV-2300027
Description	Dayvigo
Strength	All
Change Description	Address Change
Component Type	Leaflet
Dimensions	395 x 696 mm
Keyline Reference	LEAF020 V 07
Varnish	
Market(s)	NON EU: SINGAPORE
Language(s)	English
Barcode Type	;
Pharmacode	4981
Proof By	SBL
Proof Number	1
Main Body Font Size	9pt
Printed Colours	1
Date	23/05/2023

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